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Pathophysiology of Migraine

Migren Patofizyolojisi

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ABSTRACT

Migraine is a serious health problem which impair quality of life. It is the second most common primary headache that affects approximately more than %10 people in general population. Migraine pathophysiology is still unclear. Increasing results of studies suggest to migraine pathophysiology is related with primary neuronal mechanisms. Migraine pain starts in which region of brain and what brain regions are activated in different stages is unenlightened. There is evidences that growing number of studies which using new imaging techniques as positron emission tomography (PET) and functional magnetic resonans imaging (fMRI) show that migraine and cluster headaches are related with neuronal structures and vasodilatation. There are four phases to a migraine. The prodrome phase, aura, the attack, and the postdrome phase. Some datas obtained from last ten years indicate that cortical excitability has increased in interictal phase too. For many years, studies in rodents show trgimenial nerve is activated and it leads to vasodilatation and neurogenic inflammation in the headache phase. Although the majority of patients encountered in clinical practice are migraine without aura or chronic migraine, experimental studies of the migraine pathophysiology are focusing on the aura model which is used cortical spreading depression. *(Archives of Neuropsychiatry 2013; 50 Supplement 1: S1-S7)*

Key words: Migraine, aura, cortical spreading depression, cortical excitability, trigeminovascular system

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ÖZET

Migren, yaşam kalitesini bozan ciddi bir sağlık problemidir. Primer baş ağrılarında ikinci sıklıkta görülen migren, genel populasyonun yaklaşık %10'undan fazlasını etkilemektedir. Migren patogenezi hala belirsizliğini korumaktadır. Giderek artan çalışma sonuçları migren patofizyolojisinin primer nöronal mekanizmalarla ilgili olduğunu düşündürmektedir. Migren ağrısının hangi beyin bölgesinden başladığı ve farklı migren evrelerinde hangi beyin bölgelerinin aktif olduğu aydınlatılamamış bir konudur. Pozitron emisyon tomografi (PET) ve fonksiyonel manyetik rezonans (fMR) gibi yeni görüntüleme yöntemleriyle birlikte migren ve küme baş ağrılarının nöronal yapılarla ilgili olduğunu ve damar dilatasyonu ile ilgisini gösteren artan sayıda kanıtlar bulunmaktadır. Migren kliniği prodrom, aura, baş ağrısı ve postrom dediğimiz 4 ayrı evreden oluşmaktadır. Son on yılda elde edilen bazı veriler interiktal dönemde de beyin aktivitesinin uyarılabilirlik yönünde arttığına işaret etmektedir. Uzun yıllardır kemirgenlerde yapılan çalışmalar ise baş ağrısı evresinde trigeminal sinirin aktive olduğunu ve buna ikincil damarlarda genişleme ve nörojenik inflamasyon olduğunu göstermiştir. Klinik pratikte karşılaşılan hastaların büyük çoğunluğu aurasız migren, kronik migren hastaları olmakla beraber patofizyolojiye ait deneysel çalışmalar aura modeli olarak kullanılan kortikal yayılan depresyon üzerine odaklanarak gitmektedir. (*Nöropsikiyatri Arşivi 2013; 50 Özel Sayı 1: S1-S7)*

Anahtar kelimeler: Migren, aura, kortikal yayılan depresyon, kortikal eksitabilite, trigeminovasküler sistem

Çıkar çatışması: Yazarlar bu makale ile ilgili olarak herhangi bir çıkar çatışması bildirmemişlerdir.

Introduction

Migraine is a severe health problem which is the second most common one among the primary headaches, which affects more than 10% of the general population and which affects the quality of life negatively (1). The prevalence of life-time migraine in Turkey has been found to be 16% (10.9% in men and 21.8% in women) (2). The pathogenesis of migraine is stil unclear. The increasing results of studies suggest that the pathophysiology of migrain is related with primary neuronal mechanisms.

It was impossible to demostrate that primary headaches were not structural before new imaging methods including positron emission tomography (PET) and functional magnetic resonance imaging (fMRI). Wtih these methods, increased evidence has been found indicating that migraine amd cluster headaches are related with neuronal structures and vascular dilatation.

It is not clear how and from which area of the brain the migraine pain starts and which brain areas are active in the different stages of migraine. The clinical picture of migraine is composed of 4 different stages including the prodromal stage, aura stage, headache stage and postdromal stage and some evidence obtained in the last ten years indicate that the brain activity is increased in direction of exitability also in the interictal period. In addition, the effect of the aura stage to initiate pain is controversial and detailed studies show that most patients have headache during aura.

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In the profromal stage, symptoms related with the brain stem nuclei and limbic system occur. It is accepted that the aura stage during which visual, sensory and motor transient neurological deficits are observed frequently arises from the cortex. Studies which have been conducted in rodents for long years have shown that the trigemila nerve is activated in the headache period and vasodilatation and neurogenic inflammation secondary to this activation occur. In human studies, these hypotheses proposed could not be proven. Aura on which studies have been intensified and controversial issues persist, cortical spreading depression and brain stem structures will be emphasized In the pathophysiology. Although the majority of patients encountered in clinical practice have migraine without aura and chronic migraine, experimental studies related with pathophysiology are emphasized on the cortical spreading depression which is used as the aura model.

Migraine Aura

Aura is a transient neurological deficit which is observed before headache in 20% of the patients with migraine. Although visual aura (including visual hallucination) is observed most commonly, sensor yor motor auras may also be observed (3). The symptoms of visual aura spreas along the cerebral cortex and typically occurs with positive phenomenon (syntillations) following negative symptoms (scotoma).

Harold G. Wolff who is the leader of vascular theory in migraine stated that aura symptoms were related with cerebral vasoconstriction and headache was related with vasodilatation (4).

Lashley showed that the origin of visual aura was the opposite occipital cortex in 1941 and calculated that the symptoms spread at a speed of 3-5 mm/min (5). This phenomenon is related with Leao's depression waves in the cerebral cortex (6, 7). He defended that it was related with Leao's spreading cortical depression phenomenon and brought out the neuronal theory in migraine.

fMRI studies have shown that the visual aura symptoms in migraine are related with blood flow change in the occipital cortex (8,9). With use of fMRI technique occipital cortex activation was observed by visual stimulation. In the study performed by Cao et al. in 1999, migraine was triggered visually in 50% of the subjects and the events in the early period of the attack were evaluated primarily (10). Headache did not develop in any of the 6 controls and normal BOLD signals were obtained in visual activation. Headache triggered with visual stimulus was observed in 6 patients with migraine with aura and in 2 patients with migraine without aura and visual changes accompanied in 2. Before headache supression in the brain activity which progressed continuously was observed in the occipital cortex at an interval of 3-6 mm/min. Increased intensity which indicated tissue hyperoxigenation and vasodilatation accompanied this neuronal supression. In the study performed by Hadjikhani et al. (9) in 2001, it was shown that the same changes occured in spontaneous migraine with aura on fMRI as observed in the study of Cao et al. (10). In the fMRI study performed by Hadjikhani et al., it was shown that hyperemia occured following focal oligemia and spread anteriorly independent of the vascular areas. Disruption of the blood flow and its spreading anteriorly correspond to the aura symptoms and peripheral movement in the retinotopic organization in the occipital cortex (9). This increased intensity which indicates tissue hyperoxigenation was also demonstrated in experimental cortical spreading depression (11). Wood et al. showed that the same spreading events were present on PET in a migraine attack without aura, though this was a single case (12). These spreading events accompanied headache which was triggered visually independent of presence or absence of visual change. The cortical spreading dperession mechanism in migraine was confirmed with these studies and these studies do not clearly support ischemia in migraine aura.

In another perfusion-weighted imaging (PWI) study, 128 attacks were visualized in 9 patients with migraine with aura (13). In patients with migraine with aura with visual defect, it was shown that the blood flow decreased relatively in the contralateral occipital cortex, but no change occured in the other brain areas except fort he occipital cortex. No change in the blood flow was observed in patients with migraine without aura.

Cortical Spreading Depression

Cortical spreading depression (CSD) is thought to be related with massive depolarization of neuronal membranes in the gray matter and extraordinary exitability in ion change status (14). It was shown that spreading depression waves to which neuronal, glial and vascular cells participated affected the cerebral cotex visibly (15, 16). Depolarization which occurs in the brain parenchyma causes to release of vasoactive and nociceptive ions including potassium, hydrogen, nitric oxixde, glutamate and arachidonic acid metabolites (17, 18).

Neuronal firing induced by cortical spreading depression reaches its peak in 20 minutes followinf cortical spreading depression. In addition, it was shown that CSD caused to a decrease in activation of matrix metalloproteinase 9 in the pia-glial barrier and cerebral cortex and a decrease in lamin and other markers in the blood-brain barrier and compartmental barrier (19). It was also shown that nociceptive molecules including HMBP1 released during CSD in rodents mediated activation of the trigeminal nerve (19). Conclusively, studies performed in rodents showed that CSD waves triggered trigeminal vascular fibers and caused to lateralized pain (15, 20). Additionally, CSD activates the trigeminovascular system by causing to various cellular and vascular changes in the meningeal membrane (pia mater, arachnoid mater and dura mater) (15).

There are fMRI studies showing that CSD contributes to complex vascular phenomena in patients with migraine. It was found that spreading depression was related with mutliphasic vascular response in mice. Dilatation in cortical superficial vessels may spread along the vessels due to intrinsic vascular mechanism (20). Afterwards, following regional vasodilatation the diameter returns to the normal value and vasoconstriction occurs (20, 21). As a response to CSD the presence of vasoconstriction in the superficial components may vary according to species and methodologies. In humans, hypoperfusion with vasoconstriction was shown by fMRI studies in patients with migraine with aura an deven without aura (10, 22, 23). In in vivo imaging studies, it was shown that astrocytes with CSD and calcium waves initiated vasoconstriction in rodents (24).

Migraine and Cortical Exitability

There are clinical electrophysiological studies showing cortical exitability changes in migraine. In many studies, an increase in the amplitude of cortical evoked potentials and a decrease in habituation was shown in the interictal period in patients with migraine compared to controls and these differences disappeared in the ictal period (25). In other studies, a decrease in the threshold

of phosphene formed with transcranial magnetic stimulation (TMS) was shown in patients with migraine (26, 27, 28). TMS application to the occipital cortex in order to evaluate the underlying exitability in spontaneous migraine aura or migriane aura triggered visually may be more relevant in terms of migraine (29). In a study which evaluated the formation of phsphenes by applying TMS to the occipital cortex, it was found that the threshold of phosphene formation was low in patients with migraine with aura and was related with hyperexitability in the occipital cortex (30). In patients with migraine, a decrease in visual accuracy supression induced by TMS was shown (31). While the sensorial cortex gave excessive reaction to repetetive stimuli in patients with migraine, normal habituation was observed in healthy controls in contrast. In addition, distupted cortical inhibitor responses and marked intracortical fascilitation were reported şn patients with migraine (32, 33).

There are many srudies investigating the motor cortex by using TMS in patients with migraine. In three studies, the motor cortex was examined and increased exitability was found in patients with migraine in 2 studies. It was thought that these neurophysiological findings were involved in the mechanism of migraine (34, 35).ın the study in which patients with migraine with and without aura were compared with controls, it was shown that the motor threshold was increased in migraine (35). These findings indicate increased cortical exitability or decreased inhibition in patients with migraine.

In addition, there are also studies suggesting that the cortical exitability is decreased in migraine in contrast to the known fact (36). The difference here might have arised from the difference in the methodologies of the studies. Another explanation may be the difference in exitability in time in patients with migraine. With this view, differences in the threshold of formation of phosphene were observed with repetetive TMS stimuli in patients with migraine compared to controls (37). This suggests disregulation of cortical exitability in patients with migraine independent of presence of increased or decreased cortical exitability (36, 38). Abnormal change in cortical exitability may play a role in explaining different symptoms of patients with migraine.

For cortical spreading depression to initiate a change in the exitability in the cerebral cortex must occur. Glial cells play a key role in change of cortical exitability in migraine. There is evidence indicating that mutation of Na+/K+ ATPase primaily expressed in astrocytes is responsible in familial hemiplegic migraine type 2 (39,

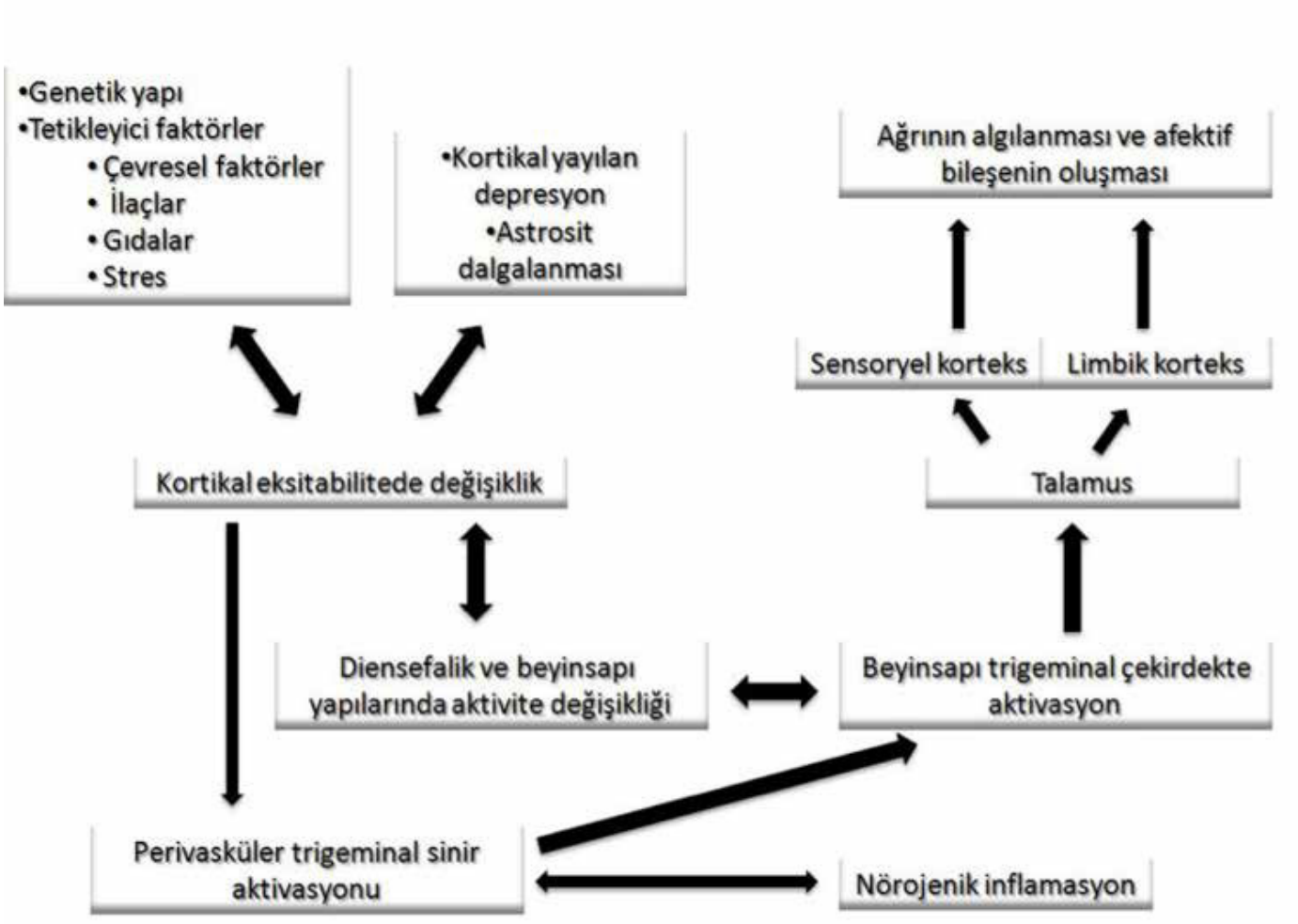

Figure 1. Brief diagram of the pathophysiology of migraine

40). In vitro studies suggest that this mutation increases exitability by increasing extracellular potassium with decreased enzyme functions (40, 41). This view was supported with studies conducted with pharamcologicalagents initiating cortical spreading depression including potassium, glutamate, NMDA and NA+/K+ ATPase inhibitor ouabain (42, 43).

Migraine and the Brain stem

There are strong findings indicating that the brain stem has an important role in the pathophysiology of migraine. Symptoms including nausea, vertigo and autonomic symptoms are thought to arise from the brain stem.

PET screening showed an increase in cerebral metabolism in the brain stem compared to the other areas in 10 patients with migraine (31). In addition, it was shown that the cerebral metabolism was decreased in the parietal area including the medial frontal and somatosensorial cortex. This suggests that the normal inhibitory effect of higher cortical centers is decreased and the activity of the brain stem is increased in pain pathways in patients with chronic migraine. Because of anatomical localization defect of PET it is thought that activation occurs in the dorsal raphe nucleus, periaquaductal grey matter (PAG) and locus coeruleus (44). There is a single case report reporting activation of red nucleus and substantia nigra in spontaneous migraine attack (45). The same investigators found that the red nucleus and substantia nigra were also activated in migraine triggered visually (46). It is known that the red nucleus and substantia nigra have functional role in motor control. The red nucleus is also related with pain and nociception (47). In many animal studies, the red nucleus was shown to be involved in sensory and noxious stimulation. Ipsilateral red nucleus activation was shown in pain induced by capsaicin. It is stil not known if the red nucleus is involved in pain pathways or in motor response to pain.

fMRI studies show that the brain stem and especially the dorsolateral pons is activated during migraine attacks (48, 49, 50). It is thought that brain stem dysfunction due to activation of the dorsal pons and PAG during migraine attacks plays a role as a generator in migraine pain (51, 52). PAG and other neuromodulator structures including rostral ventromedial medulla, locus coeruleus, raphe nucleus are primarily involved in modulation of nociception (53). Imaging studies have shown that PAG is a prat of the descendent pathway in high cortical control in pain modulation (54). PAG has a great role im nociceptive pathways in connections coming from the thalamus, hypothalamus and autonomic nervous system. PET and fMRI studies have shown that the metabolism and function of the brain stem is changed in patients with chronic migraine (31, 55). In an interictal imaging study, it was shown that dysfunction of PAG increased as the chronicicity of migraine increased (56). In a study performed with PET in migraine, it was found that PAG was hyperacitve (48). The ventrolateral lower part of PAG has an important role in modulation of trigeminal nociception (57). It has been shown that hyperactivity of the nociceptive system has a genetic predisposition (58). It was found that o-agatoxin-IVA which is a P/Q channel blocker administerred into the ventrolateral PAG of rats by microinjection fascilitated neuronal activity in the trigeminal nociceptive pathway (57). This study showed the effect of both P/Q tyep calcium channels and PAG in trigeminal proprioception. In another study, electrical stimulation of PAG was shown to cause to headache (59).

In addition, there are many publications suggesting that structural lesions in the brain stem cause to headache (60, 61, 62).

In fMRI studies, many brain areas were found to be related with nociception during migraine attacks (44, 63, 64), but it is not clearly known where the first activation is initiated in the nociceptive pathways.

Trigeminovascular System

It is accepted that the trigeminovascular system plays an important role in headache. This fidning is based on the fact that the vessels innervated by the trigeminal way cause to headache in patients with an open consciousness, while stimulation of the brain parenchyma does not lead to any discomfort (65, 66).

The trigeminal nerve and ophtalmic nerve play an important role in transportation of pain impulses from the intracranial structures (67,68). According to the data obtained from rodents, neurogenic inflammation in the dura mater, plasma protein extravasation, increased blood flow and vasodilatation play an important role in the headache phase (69). In the characteristic headache phase, CSD was found to have an important role in trigeminovascular activation and neurogenic edema (15). CSD cause to an increase in the blood flow in the arteries supplying the dura mater by way of the trigeminal nerve. In anesthetic rodents, the blood flow in the middle meningela artery reaches a peak in 20 minutes following cortical spreading depression and the blood flow returns to normal in 50 minutes. In addition, cortical spreading depression induces trigeminal nerve mediated plasma protein extravasation in the ipsilateral dura mater in rodents. It was shown to induce secondary neurons in peripheral changes by demonstrating c-fos staining in the ipsilateral superficial nociceptive lamina (15, 70).

One of important mediators in plasma protein extravasation is nitric oxide (NO). NO is released from the vascular cells in response to constriction. Migraine can be triggered by nitroglycerine infusion. With this induction, headache starts 4-6 hours later (71). It is thought that the underlying mechanism of this includes delayed inflammatory response in the dura mater, increase in iNOS expression and upregulation of proinflammatory cytokines including IL-1 and IL-6 (72). In another theory, fluctuation in NO may lead to migraine pain by activating the trigeminal vascular system independent of plasma protein extravasation without the contribution of cortical structures.

Vasoconstiction related with cortical spreading depression and/or astrocyte calcium fluctuations may lead to a change in the metabolic activity and blood flow. Decreased parenchymal blood flow causes release of cellular metabolites by affecting the neuronal glial activity and triggers the nociceptive response by decreasing extracellular pH. For example, transient receptors in nociceptive trigeminal neurons or change in ion channels may be activated in these conditions (73).

Trigeminal neurons innervate the meninges in many ways including visceral sensory neurons (74). The relation between triggering of sensory neurons by specific stimuli and occurence of migraine pain is not clear. Additional factors may also be responsible; mechanical compression, ion changes in the extracellular space (increased potasssium, increased osmolarity, decreased pH), neuropeptides (bradykinin, substans P, endothelin, calcitonin gene-related peptide (CGRP), neurotransmitters (glutamate, serotonin, histamin, adenosine triphosphate (ATP), adenosine) eicosanoids

and NO. The subunits of the trigeminal neurons may give specific responses with different stimuli at different thresholds (75).

In addition, recent studies have shown that astrocytes affect both neuronal and vascular activity by playing a role in intracellular signalling. Astrocytes affect the neuronal activity by expressing many neurotransmitter receptors (76). On the other hand, glutamate which modulates neuronal function provides transmitter release including ATP (77). Astrocytes wrap the vessels with their feet close to the vascular cells. Astrocyte signal affects the vascular tonus directly and causes to vasoconstriction or vasodilatation depending on release of eicosanoid, potassium and ATP (78, 79, 80).

Conclusively, CSD and intrinsic brain prenchymal events cause to lateralized pain by triggering the trigeminovascular fibers.

The role of the activation of the trigeminovascular system supports the change due to perivascular trigeminal nociceptive inhibition with the effect of triptan and recently CGRP antagonist effect. With detection of the binding sites of the primary afferents in the human brain stem to the 5HT1B/D agonists in the central system, the importance of the tirgeminovascular system has increased further (81, 82). Other migraine therapies including ergotamine have been proposed to affect primarly the peripheral trigeminal vascular complex as well as central mechanisms (83). CGRP is accepted to be an important mediator in migraine and is released to protect the vascular tonus as a response to vasoconstiction in the perivascular neurons. It was shown that neurons containing CGRP were present in the central and peripheral nervous system (including trigeminal nucleus caudalis in the brain stem) and contituted an alternative source for release of CGRP during migraine attacks (84, 85, 86, 87). The role of the trigeminovascular system is supported by observation of an increase in CGRP which is involved in cerebral vasoregulation in the jugular vein during migraine attakcs. (88)

Interestingly, trigeminal risotomy was not efficient in preventing migraine of cluster headache, although the sensory function of the trigeminal nerve was disrupted (89). With this result, headache in the absence of peripheral trigeminal input in the ipsilateral side suggests the probable response of the nociceptive pathways.

Conclusion

Migraine attack occurs with neuronal and vascular changes in which CSD, cortical exitability and the trigeminovascular system are involved. The pathophysiology of migraine has not been elucidated fully yet. Especially migraine without aura, chronicity, the relation of C-fibers mediated pain with the brain cortex, subcortical structures and brain stem, neuropeptide contents and general trigerring responses including NO need to be examined in detail and experimental studies should be performed in a translation fashion.

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